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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,275	05/09/2007	M. Ian Phillips	USF-199/TCXZ1	9704
23557 7590 07/14/2009 SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614			EXAMINER SAJJADI, FEREDOUN GHOTB	
			ART UNIT 1633	PAPER NUMBER
			MAIL DATE 07/14/2009	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/567,275

**Applicant(s)**

PHILLIPS ET AL.

**Examiner**

FEREYDOUN G. SAJJADI

**Art Unit**

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 May 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-28 is/are pending in the application.
- 4a) Of the above claim(s) 1-16, 27 and 28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17-26 is/are rejected.
- 7) ☒ Claim(s) 17 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 February 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/003)  
Paper No(s)/Mail Date 5/19/2008
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Applicants' response dated March 9, 2009 to the restriction requirements of February 9, 2009, and the supplemental response dated May 12, 2009 have been entered. Claims 18 and 19 have been amended. No claims were cancelled or newly added. Currently, claims 1-28 are pending in the application.

#### ***Election/Restrictions***

Applicants' election of Group III (claims 17-26), drawn to a method of targeting a stem cell to a target tissue in a subject by *ex vivo* cell therapy, the method comprising administering to the target tissue a composition comprising: (a) a first polynucleotide comprising: (1) a gene switch/biosensor comprising a nucleic acid sequence encoding a physiological stimulus-sensitive chimeric transactivator, and (2) an operatively linked tissue-specific promoter; and (b) a second polynucleotide comprising a nucleic acid sequence encoding a stem cell- attracting chemokine, is acknowledged. The election was made without traverse. Applicants' species election of heart as the target tissue, viral vectors, MLC-2v as the tissue-specific promoter and hSDF-1 as the stem cell attracting chemokine, is further acknowledged. Accordingly, claims 1-16 and 27-28, have been withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions.

The election requirement is deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.). The instant claims have been examined commensurate in scope of the elected invention and the species of the invention.

Claims 17-26 are under current examination.

### ***Information Disclosure Statement***

The information disclosure statement (IDS) submitted on May 19, 2008 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner, and indicated as such on IDS form PTO-SB/08A.

### ***Claim Objection***

Claim 17 is objected for requiring the particulars of a withdrawn claim. Claim 17 requires the composition of claim 1. The objection may be obviated by amending the claim to recite the particulars of claim 1.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-22 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.: 2002/0094327; effective filing date: Nov. 5, 2000), in view of Phillips et al. (Hypertension 39(part 2):651-655, 2002), and further in view of Tang et al. (Hypertension, 39(part 2):695-698, 2002).

The claims encompass a method of targeting a stem cell to the heart of a subject by *ex vivo* cell therapy, the method comprising administering to the heart tissue a composition comprising: (a) a first polynucleotide comprising: (1) a gene switch/biosensor comprising a nucleic acid sequence encoding a physiological stimulus-sensitive chimeric transactivator, and (2) an operatively linked MLC-2v cardiac promoter; and (b) a second polynucleotide comprising a nucleic acid sequence encoding the stem cell- attracting chemokine hSDF-1.

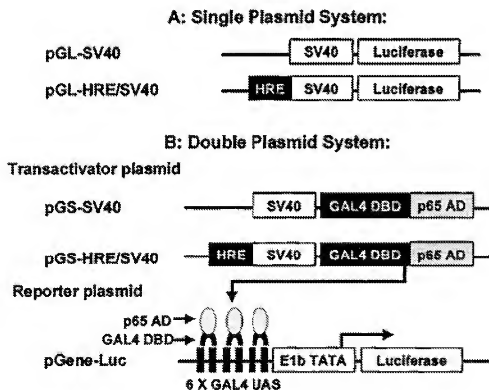
Petersen et al. describe a method of modulating the targeting of pluripotent stem cells to a target tissue of a mammalian subject by increasing the concentration of SDF-1 alpha protein in the target tissue (Abstract). The mammalian subjects include humans and non-humans (paragraph [0063], limitation of claim 17), and the target tissue can be the heart (paragraph [0063], p. 8, limitation of claim 19). Peterson states that the mammalian SDF-1 alpha genes, including the human gene are known (paragraph [0030], and may be used as part of a heterologous DNA under the control of a tissue-specific promoter (paragraph [0086]), using AAV-based vectors (paragraph [0084], limitation of claim 18). *Ex vivo* gene transfer of the SDF-1 alpha nucleic acid under the control of a tissue specific promoter to host cells, followed by delivery of the transfected cells to the host is described in paragraph [0104], p. 13 (limitation of claim 20). In Example 2, Petersen et al. describe SDF-1 alpha expression in a model of tissue injury (p. 14, limitation of claim 25). The authors additionally describe using agents that increase the transcription or translation of a gene encoding SDF-1 alpha in a target tissue, that may also be used in the invention (paragraph [0068], p. 9; limitation of claim 24), or using agonists (claim 1, p. 14), or G-CSF to increase the number of stem cells in the peripheral blood (paragraph [0009], p. 1).

While Peterson et al. do not describe expressing their tissue specific SDF-1 alpha gene expressed via a heart promoter operably linked to a gene switch/biosensor, such was known in the prior art.

Phillips et al. describe a vigilant vector comprising a heart-specific promoter (MLC2v) operably linked to a hypoxia response element and a therapeutic gene in an AAV vector, for cardioprotection (Title, Abstract and Figure 1). Phillips et al. additionally disclose a double plasmid approach that produces a powerful chimeric transcription factor consisting of the yeast transcription factor GAL4 DNA binding domain and the p65 transactivation, that when combined with HRE and SV40 promoter, increased gene expression 400-fold when activated by hypoxia (first column, p. 654).

The double plasmid system is further described by Tang et al., stating that coronary artery disease frequently involves repeated bouts of myocardial ischemia (thus at increased risk of damage; limitation of claim 26), and to automatically up-regulate the cardioprotective transgenes under hypoxic ischemia, a "vigilant vector" gene therapy system was developed and tested in a

rat embryonic cardiac myoblast (H9c2). Tang et al. disclose that, in the vigilant vector, a hypoxia response element-incorporated promoter was used as a switch to turn on the gene expression in response to hypoxic signal. Furthermore, Tang et al. state that a novel double plasmid system was designed to elevate the potency of the vigilant vector, and instead of putting the promoter and the reporter gene in the same plasmid (single plasmid system), Tang et al. separated them into two plasmids: the transactivator plasmid and reporter plasmid (double plasmid system). Tang et al. state that the hypoxia response element (HRE)-incorporated promoter increased the expression of a chimeric transcription factor consisting of the yeast GAL4 DNA binding domain and the human nuclear (transcription) factor-  $\kappa$ B (NF- $\kappa$ B) p65 activation domain, and the chimeric regulator binds specifically to the upstream activating sequence for GAL4 in the reporter plasmid and activates the transcription of the transgene (Abstract and Figure 1 shown below:



Tang et al. state that the system provides a promising way to improve the activity of other ubiquitous and tissue-specific promoters, thus providing the motivation to extend the system to the tissue-specific promoter expression system of Petersen et al. As the disclosure of Phillips et al., Tang et al. and Petersen are directed to increasing the expression of a heterologous nucleic acid under the control of a tissue-specific promoter, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine their respective teachings and to substitute the SDF-1 alpha gene of Petersen for the therapeutic gene of Phillips et al. as instantly claimed, with a reasonable expectation of success, at the time of the instant invention.

Claims 17 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen et al. (U.S. Patent Publication No.: 2002/0094327; effective filing date: Nov. 5, 2000), in view of Phillips et al. (Hypertension 39(part 2):651-655, 2002), and Tang et al. (Hypertension, 39(part 2):695-698, 2002), as applied to claims 17-22 and 24-26 above, and further in view of

The claims encompass a method of targeting a stem cell to the heart of a subject by *ex vivo* cell therapy, the method comprising administering to the heart tissue a composition comprising: (a) a first polynucleotide comprising: (1) a gene switch/biosensor comprising a nucleic acid sequence encoding a physiological stimulus-sensitive chimeric transactivator, and (2) an operatively linked MLC-2v cardiac promoter; and (b) a second polynucleotide comprising a nucleic acid sequence encoding the stem cell- attracting chemokine hSDF-1, and stem cells.

Petersen et al. describe a method of modulating the targeting of pluripotent stem cells to a target tissue of a mammalian subject by increasing the concentration of SDF-1 alpha protein in the target tissue (Abstract). The mammalian subjects include humans and non-humans (paragraph [0063]), and the target tissue can be the heart (paragraph [0063], p. 8). Peterson states that the mammalian SDF-1 alpha genes, including the human gene are known (paragraph [0030], and may be used as part of a heterologous DNA under the control of a tissue-specific promoter (paragraph [0086]), using AAV-based vectors (paragraph [0084]). *Ex vivo* gene transfer of the SDF-1 alpha nucleic acid under the control of a tissue specific promoter to host cells, followed by delivery of the transfected cells to the host is described in paragraph [0104], p. 13.

Phillips et al. describe a vigilant vector comprising a heart-specific promoter (MLC2v)

operably linked to a hypoxia response element and a therapeutic gene in an AAV vector, for cardioprotection (Title, Abstract and Figure 1). Phillips et al. additionally disclose a double plasmid approach that produces a powerful chimeric transcription factor consisting of the yeast transcription factor GAL4 DNA binding domain and the p65 transactivation, that when combined with HRE and SV40 promoter, increased gene expression 400-fold when activated by hypoxia (first column, p. 654). The double plasmid system is further described by Tang et al.

While Peterson et al. do not describe the co-administration of stem cells to the target tissue along with the AAV vector, such was known in the art.

Kovesdi et al. describe vectors that include polynucleotides encoding VEGF fusion proteins that promote angiogenesis and wound healing (Abstract). Kovesdi et al. disclose that the vector may be administered to any cardiac tissue of the heart (paragraph [0161], and additionally co-administered with factors such as GM-CSF, in association with the administration of stem cells (paragraph [0171], thus curing the deficiency in Petersen et al.

As the disclosure of Petersen et al., and Kovesdi et al. are directed to gene delivery to the heart of a subject and further recruitment of stem cells to the target tissue, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine their respective teachings and to co-administer stem cells with the vector of Petersen as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would be motivated to co-administer stem cells with a therapeutic polynucleotide to the heart of a subject, because such was specifically taught by Kovesdi et al. and would result in increased wound healing and tissue repair.

### ***Conclusion***

#### **Claims 17-26 are not allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREDYOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/  
Primary Examiner, Art Unit 1633